

## NIH Intramural ME/CFS Study Q&A

The manuscript on ME/CFS published in [Nature Communications](#) provides irrefutable evidence for the biological nature of the disease. Evidence shows that it is a multi-systemic disease. Major findings in support of this are: evidence of persistent immune activation in the blood and cerebrospinal fluid with differential effects in men and women, abnormalities on functional MRI of the brain, metabolic abnormalities in the cerebrospinal fluid, neurotransmitter abnormalities, oxidative stress in muscles, altered lipids with differential effects in men and women, altered gut microbiome, and dysautonomia. These findings suggest several potential therapeutic targets. The absence of structural abnormalities suggest that the course of the illness could potentially be halted or reversed. Further, a few patients who met all the criteria for ME/CFS and had been diagnosed with the disease were found to have other underlying diseases. It is important to follow these patients to make sure that another illness does not manifest itself.

Below we have addressed some of the questions we have received:

### Does the *Nature Communications* paper describe all the findings from the intramural study

A tremendous amount of data was collected during the study most of which has been made available publicly. We expect that the broader research community will analyze these data and report new findings. Some data from the intramural study are still being analyzed and will result in additional publications. Two other papers about post-exertional malaise (PEM) have already been published:

- [Characterization of Post-exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome](#) (Stussman et al., 2020)
- [Mixed methods system for the assessment of post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an exploratory study](#) (Stussman et al., 2024)

Other related publications include:

- [Beyond the symptom: the biology of fatigue](#) (Raizen et al., 2023)
- [WASF3 disrupts mitochondrial respiration and may mediate exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome](#) (Wang et al., 2023)

### Was post-exertional malaise (PEM) investigated in this study?

Yes, the NIH intramural study team investigated PEM in people with post-infectious ME/CFS (PI-ME/CFS) as it occurred over hours and days following a cardiopulmonary exercise test (CPET). The participants completed detailed qualitative interviews one hour before and at multiple timepoints, up to 72 hours, after the CPET, which asked them to describe their current physical, cognitive, and emotional symptoms. In addition, researchers collected mitochondrial function and bioenergetic data before and after the test. This allowed researchers to better understand the development, severity, and progression of PEM in real time. Although the PEM-related findings were not discussed in the current paper in detail, some have been published:

- [Characterization of Post-exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome](#) (Stussman et al., 2020)
- [Mixed methods system for the assessment of post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an exploratory study](#) (Stussman et al., 2024)

Further analysis of biological samples collected at each time period is planned.

#### Was PEM a criterion for study participants with ME/CFS?

Yes, PEM was a criterion for participation in the study. As noted in the methods section of the paper, “The PI-ME/CFS group was selected based on medical record documentation of persistent and severe fatigue and **post-exertional malaise** as the consequence of an acute infection within the last five years without a prior history of explanatory medical or psychiatric illness.” PEM was also assessed using a questionnaire, as part of a directed interview, as part of an open qualitative interview, and as part of a physician interview. Additionally, the presence of PEM was reviewed by the adjudication panel as part of their decision-making process.

#### What is effort preference?

- In our day-to-day lives, the brain must decide how to expend its focus and energy on the tasks that are presented to it. The expenditure of energy is interpreted by the brain as effort. Not all tasks require the same amount of effort, with some tasks being easier and others harder. Tasks are also not equally valuable, with some tasks having more reward and others less. Effort preference is a measurement of the decisions the brain makes of how to utilize its energy based on difficulty and value of a task. We are often not aware that these processes are happening.
- In this study, a series of tasks were given in which people with PI-ME/CFS and healthy volunteers had to choose between doing an easy or hard pushing task. The tasks were repeated many times, with different reward values assigned for successful completion. People with PI-ME/CFS were more likely to choose the easy task over the hard task compared to the healthy volunteers. This difference in task choice was not influenced by the number of tasks they performed or the value of the tasks. All the factors that did influence the choices are not known, and as is the usual case, many are not conscious.
- The full biological explanation for the observed difference in effort preference in PI-ME/CFS is not known. In the study, effort preference was related to differences in the brain, including decrease in catechol neurotransmitters and decreased activation of the right temporo-parietal junction, which plays a role in evaluating and initiating physical action. Further analysis of the relation between effort preference and these biological observations is planned.

#### Why was a reward task part of the study?

The researchers used a behavioral task designed to objectively measure task-based decision-making, and reward is always a factor in decisions. Fatigue is difficult to study because it is often self-reported. They chose this task to better understand the biological processes behind fatigue.

#### Why did you conduct a 1-day CPET instead of a 2-day CPET?

Researchers decided to use a single CPET to induce PEM after extensive conversations with experts in the field, literature reviews, and [their own focus group work](#) (Stussman et al., 2020). They also wanted to reduce stress and other harmful effects that the 2-day CPET could have had on participants. The single CPET protocol successfully induced PEM in each of the participants with PI-ME/CFS. Further, as the NIH study was using a wealth of information for diagnostic purposes—including an expert panel of clinical adjudicators to establish the ME/CFS diagnosis—researchers decided that a 2-day CPET was not necessary.

#### Why were there only 17 participants with ME/CFS?

- From the beginning, the study was designed to examine a small group of well-defined patients that could be studied in great depth and help identify the most robust biological characteristics that would distinguish them from the control populations. The NIH Clinical Center is uniquely suited for such studies and is not equipped for large-scale studies. The sample size was sufficient to see significant differences reliably between people with PI-ME/CFS and healthy controls. A larger sample size in this study would not have changed the overall results.
- Additionally, most participants were brought into the NIH Clinical Center twice for up to 2 weeks total, and researchers were typically only able to examine one participant at a time over the course of the study. Unfortunately, when the COVID-19

pandemic hit, researchers were unable to bring in new study participants. At that point, the researchers decided to look at the existing data to see if any conclusions could be derived from them and if it would be useful to make them publicly available. The researchers decided that they had collected enough data and moved on to analyzing their full dataset so they could publish the results as soon as possible.

#### Why did you not include more severe or chronically ill ME/CFS patients?

- The researchers wanted to make sure that their observations would not be confounded by comorbidities and by deconditioning which are most often present in individuals with prolonged illness. Although they did not include bedridden patients, most of the participants would be classified as severe as described in [this paper](#) (van Campen et al., 2020).
- Previous studies suggest that there are substantial differences between people who have had ME/CFS for a few years compared to those that have been chronically ill for many years. For this population, especially in a small sample size, it would be difficult to determine which findings are due to prolonged illness or if other factors contribute to the results.
- This study was very intense and involved numerous tests, sample collections, and an exercise test. Participants also had to travel to the NIH. Researchers were mindful of potential negative effects such an intensive study would have on participants with ME/CFS, especially since it was the first time such a comprehensive protocol was being used to study this disease. The research team is grateful to the individuals who participated in this study.
- The NIH research team hopes that investigators across the country will use the results as a starting point for additional studies on people with severe and/or chronic ME/CFS and develop studies that will lead to treatment trials. All the data collected in this study is available for researchers to use to conduct their own analyses.

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